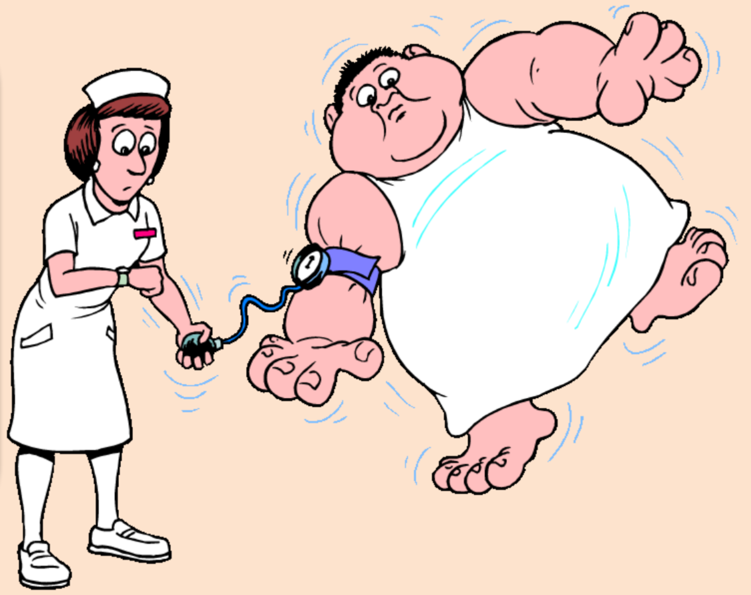
Draw Pharmacology in your mind



Regular checks
Low sodium diet
Hypertension
Management of high blood pressure
Diuretic

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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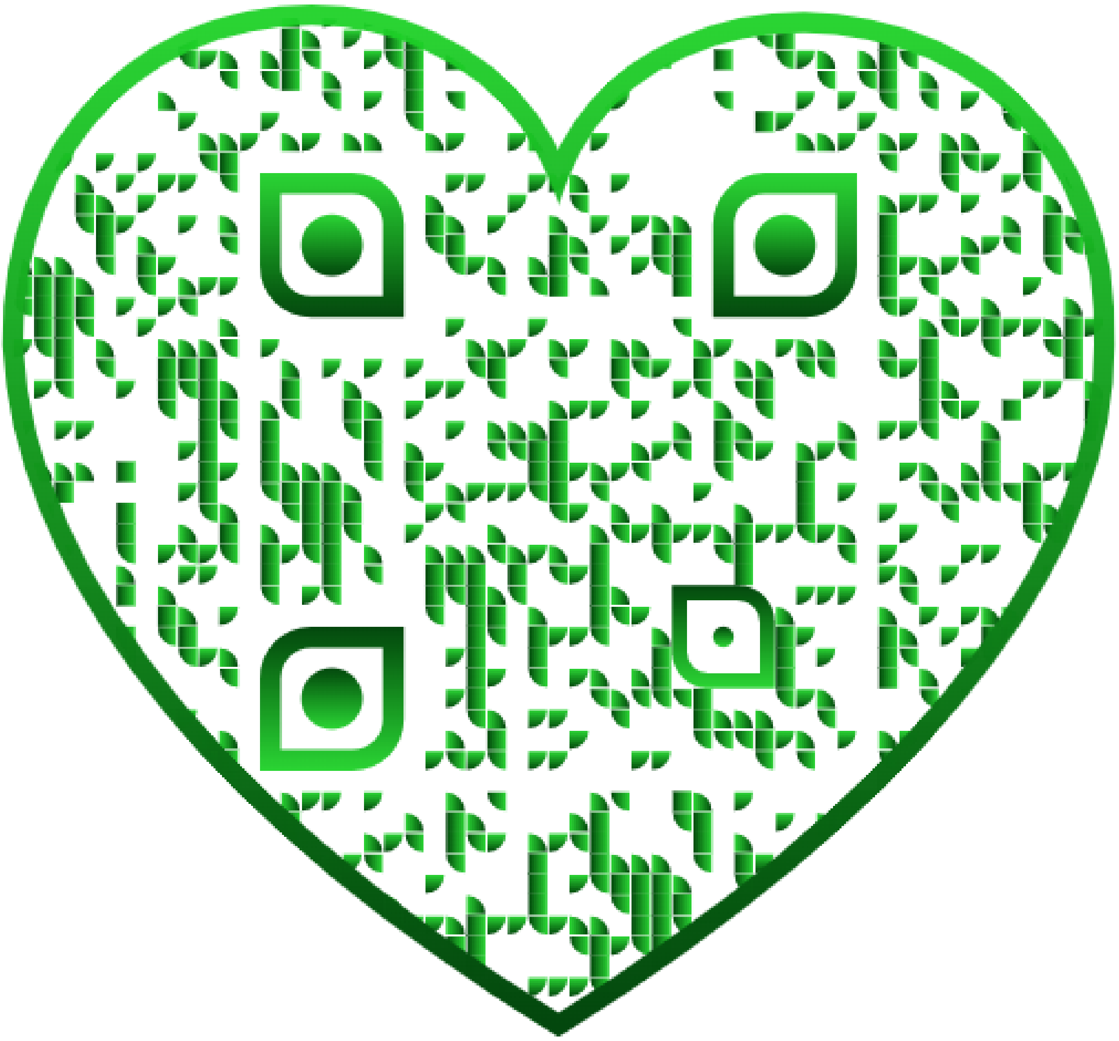
لا تنسونى من صالح دعائكم

Pharmacist. Alaa Nasr

د. آلاء نصر



1. HYPERTENSION

- Hypertension is a state of **elevated blood pressure**
- **Blood pressure (BP)** is the pressure exerted on the walls of arteries
- **Systolic BP** is the blood pressure during systole *(myocardium contraction)*
- **Diastolic BP** is the blood pressure during diastole *(myocardium relaxation)*
- **Normal arterial blood pressure:** 120-140 for systolic BP and 80-90 for diastolic BP
- **So, Hypertension = Blood pressure > 140/90**

Factors affecting blood pressure

1. Cardiac output

When CO ⇑ → Systolic BP ⇑

2. Blood volume

When blood volume ⇑ → Systolic BP ⇑
(ex. in case of renal impairment → salt and water retention → ⇑ blood volume → ⇑ venous return → ⇑ cardiac output → ⇑ blood pressure **)**

3. Peripheral vascular resistance (Blood vessel tone)

When the blood vessel are **constricted** → ⇑ peripheral resistance → ⇑ blood pressure
And when the blood vessels are **dilated** → ⇓ peripheral resistance → ⇓ blood pressure

- **Systolic blood pressure** depends on cardiac output and blood volume *(related to the Heart)*
- **Diastolic blood pressure** depends on peripheral vascular resistance *(related to blood vessels)* and is responsible for complications of hypertension

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Types of hypertension

1. According to diastolic blood pressure

1. **Mild hypertension** → diastolic blood pressure **90 -104 mmHg**
2. **Moderate hypertension** → diastolic blood pressure **104 - 120 mmHg**
3. **Severe hypertension** → diastolic blood pressure **> 120 mmHg**

# Malignant hypertension vary high diastolic blood pressure for 6 months may be lethal (causes death) !

2. According to Etiology

a) Primary (Essential) hypertension

- It represents 90% of hypertensive cases
- The cause is not known
- It is called essential as it was believed that the raised BP is essential to maintain adequate tissue perfusion

b) Secondary hypertension

It arises secondary to a primary cause either a disease or use of a drug

1) Endocrine disorders
a. Pheochromocytoma *(tumor in Adrenal gland → ⇑ catecholamines)*
b. Hyperthyroidism
c. Cushing's syndrome *(⇑ cortsone)*

2) Renal diseases
a. Glomerulonephritis
b. Urinary obstruction
c. Renal artery stenosis

3) Vascular causes
a. Coarctation of aorta (aorta congenital narrowing)
b. Atherosclerotic degenerative changes

4) Drugs
Oral contraceptives - Steroids (cortisone)

Risk factors of hypertension

1. Age: as age ⇑ tendency of hypertension ⇑

2. Gender:
a) Pre-menopause → females are less susceptible to hypertension than males
b) Post-menopause → females are equal to males

3. Pregnancy
Pre-eclampsia *(is a pregnancy-related disorder)* characterized by hypertension + edema + albuminurea

4. Diabetes
Long term uncontrolled diabetes may lead to vascular changes (vascular degenerative changes) → hypertension

5. Alcohol consumption
Alcohol release chatecholamines from adrenal medulla → hypertension

6. Smoking
may increase complications of hypertension

7. Stressful life style

8.High salt intake in diet

9. Genetic
Hypertension is 4-5 times more in black people than white

Complications of hypertension

1) Cardiac complications
Heart failure may be caused due to persistent hypertension *(⇑ peripheral vascular resistance leads to ⇑ diastolic blood pressure so, the heart must exert more work to push the blood into the constricted blood vessels)*

3) Eye complications
Retinopathy
→⇑ intraocular pressure (glaucoma)
→ retinal hemorrhage

2) Blood vessels (constriction)
a. Coronaries
Cardiac ischemia angina
b. Cerebral
Headache - Cerebral edema - Cerebral hemorrhage - Thrombosis (may lead to hemiplegia or stroke)
c. Renal
ischemia causes renal failure

Renal failure ⇄ **Hypertension**

Therapy of hypertension

1. Non-pharmacological therapy

1) Weight reduction
- in obese and mild hypertensive patients
- loss of 1 Kg = decrease 2-3 mmHg in blood pressure
- Weight loss causes

⇓ blood volume → ⇓ venous return → ⇓ cardiac output

2) Salt restriction
- 70 mEq of Na^+ per day
- Moderate salt restriction = decrease 7 mmHg in diastolic blood pressure
- It does not decrease BP in all hypertensive patients however it is recommended even for non-responding patients as salt may antagonize the effect of antihypertensive drug such as diuretics
- Salt intake causes

⇓ Na^+ → ⇓ water retention → ⇓ blood volume → ⇓ cardiac output → ⇓ blood pressure

3) Reduction of alcohol consumption
4) Stop smoking
5) Exercise
6) Avoid stressful conditions

2. Pharmacological therapy

1) Sympatholytics
1. Centerally acting
2. Ganglionic blockers
3. ANB
4. α blockers
5. β blockers

2) Vasodilators
1. Arterial vasodilators
2. Mixed vasodilators

3) Drugs acting on RAS
1. ACE inhibitors
2. AT_1 receptor antagonists

4) Diuretics

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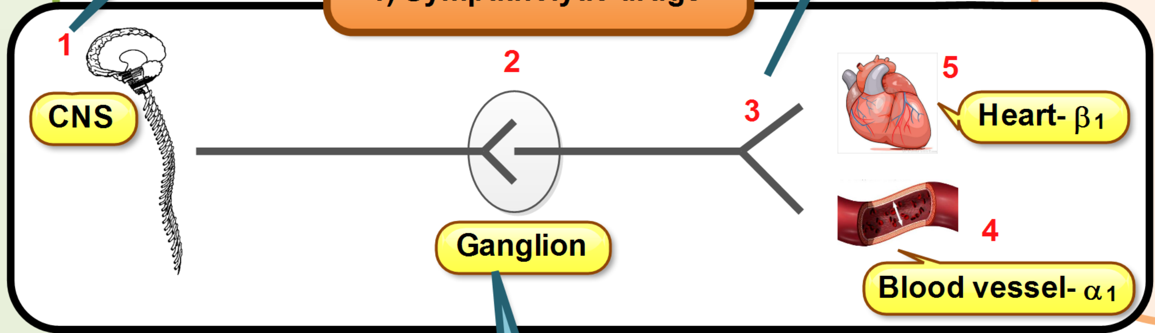
1) Sympatholytic drugs



1. Centrally acting drugs (α_2 adrenoceptor agonists)

- **α-methyl dopa** (Aldomet®) - **Clonidine** (Catapress®)
- **New generation : Moxonidine** (Cynt®) - **Rilmenidine** (Hyperium®)

ALDOMET
Catapres® 100
Boehringer Ingelheim
HYPERIUM 1 mg
Cynt® 0,3
Solvay Pharmaceuticals

Mechanism of action

1. Main mechanism

Stimulation of central α_2 receptors → ⇓ sympathetic outflow from CNS → ⇓ Noradrenaline release .. so causes:

- Vasodilatation (⇓ peripheral vascular resistance) leading to ⇓ blood pressure
- ⇓ Heart rate → ⇓ cardiac output → ⇓ blood pressure

2. Activation of presynaptic α_2 receptors → ⇓ Noradrenaline release from sympathetic nerves

3. ⇓ Noradrenaline release (which normally activate β_1 receptors in juxtaglomerular apparatus) → ⇓ **renin release** → ⇓ angiotensin II leading to:

- Vasodilatation → ⇓ blood pressure
- ⇓ Aldosterone → diuresis

4. α-methyl dopa is metabolized by decarboxylation to **α-methyl noradrenaline** which is:

- a **false** neurotransmitter
- activates α_2 receptors → ⇓ Noradrenaline release

# So, has a delayed onset of action than clonidine

Side effects

1. Dry mouth

2. Sedation
due to stimulation of α_2 receptors in locus ceruleus (area in the brain responsible for alertness)

3. Salt and water retention upon prolonged use of **clonidine** and **α-methyl dopa** → so the **solution** is to use **diuretic**

4. Rebound phenomenon / Rebound hypertension
Sudden withdrawal of **clonidine** causes blood pressure to shoot up ⇑⇑ much higher than pretreatment level leading to **hypertensive crisis**, **Why?**

a. Immediate and excessive increase in sympathetic activity following sudden withdrawal of clonidine
b. Upregulation of postsynaptic α_1 receptors which develops due to decreased sympathetic activity during clonidine use
Solution: Gradual withdrawal of clonidine

Rebound hypertension less commonly occur with other α_2 agonists (α-methyl dopa - Moxonidine - Rilmenidine)

# Newer generations causes **less** sedation and dry mouth than older drugs

3. Adrenergic neuron blockers (ANB)

HYPOTEN
ANTIHYPERTENSIVE
NOVARTIS
Brinerdin®

Guanethidine

Mechanism of action

Taken by sympathetic nerve terminals → **displaces NA from storage vesicles** so
- it causes initial increase in blood pressure
- then inhibits further release of NA upon neuronal depolarization

Side effects

1. Orthostatic hypotension
2. Failure of ejaculation
3. Diarrhea
4. Nasal congestion

Rarely used now in the treatment of hypertension

Reserpine

Mechanism of action

1. Depletion of catecholamines and serotonin (5HT) in ***CNS and peripherally*** by **damaging and disintegration of storage vesicles**
2. Inhibit granular storage of NA leading to its metabolism by MAO

Side effects

1. Drowsiness and sedation
2. Depression and suicide — in 25% of patients so reserpine is **contraindicated** in patients with history of depression
3. GIT ulceration and hemorrhage — Experimental tool to induce ulcers in rats
4. Weight gain

To minimize side effects, reserpine is given in small doses in combination with other antihypertensive drugs such as diuretics or β blockers

2. Ganglion blockers

Trimetaphan - Mecamylamine - Pempidine

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Mechanism of action

They block ganglionic N_N (Nicotinic neuronal) receptors so, they block sympathetic tone to blood vessels leading to vasodilatation → ⇓ blood pressure

Uses

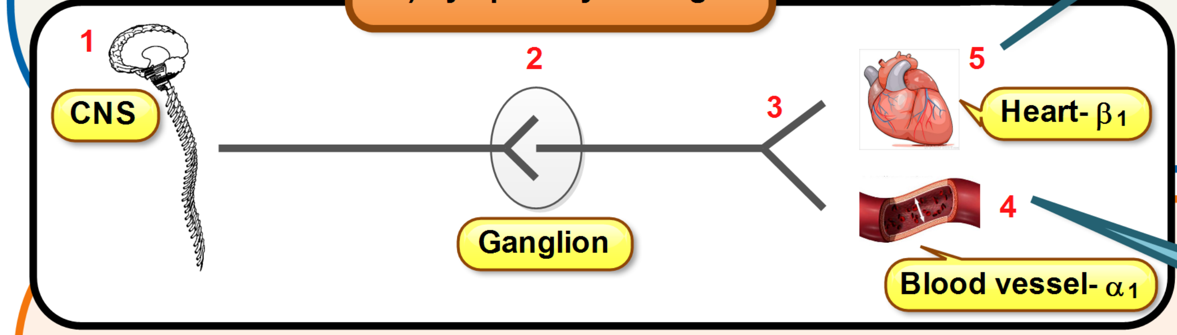
1. Hypertensive emergencies
a) Hypertensive crisis
b) Resistant / Refractory hypertension (does not respond to other treatments)
2. Used during long surgical operations such as plastic surgeries, neurosurgeries and cardiac surgeries to decrease bleeding from open wounds by producing **controlled hypertension**

# Their use is very limited due to serious side effects !

Side effects

1. CVS side effects
a) Orthostatic / Postural hypotension
b) Tachycardia
2. GIT side effects
a) Dry mouth
b) Paralytic ileus
3. Urine retention
4. Sexual dysfunction
a) Failure of erection (impotence)
b) Failure of ejaculation

1) Sympatholytic drugs


1
CNS
2
Ganglion
3
5
Heart- β_1
4
Blood vessel- α_1

5. β adrenergic blockers

Mechanism of action

β blockers decrease blood pressure by
1. blocking β_1 receptors in the heart → ⇓ heart rate → ⇓ cardiac output
2. blocking β_1 receptors in juxtaglomerular cells → ⇓ renin release → ⇓ angiotensin II
3. blocking presynaptic β receptors → ⇓ NA release from sympathetic nerves
4. blocking central β receptors → ⇓ central sympathetic outflow

1) Non selective β blockers

Propranolol (Indral®) - **Sotalol** (Betacor®) - **Nadolol** - **Timolol**

Betacor
Antiarrhythmic β-blocker
30 Tablets

INDERAL
tablets 40 mg
50 Tablets

2) β blockers with ISA

Pindolol

3) Selective β_1 blockers

Atenolol (Tenormin®, Atelol®, Blokium®, Ateno®)
Acebutalol
Metoprolol (Betaloc®)
Bisoprolol (Concor® ,Bisocard®, Bistol®)

TENORMIN
tablets 50mg
Bistol plus
5
12.5 mg
BLOKIUM 100
ATENO
50 mg
ATELOL
Betaloc
100 mg
Concor 5
Bisocard

Side effects

1. Cardiac complications
a) Sudden withdrawal of β blockers causes
- Cardiac arrhthmia
- Angina
- Myocardial infarction
- May lead to death !

b) Heart failure due to bradycardia (solution !!)

So β blockers must be gradually stopped → over 1 - 2 weeks

2. Bronchial asthma
Non-selective β blockers may cause bronchospasm → due to blocking of β_2 receptors in lungs

Potentiation of the hypoglycemic activity of insulin and oral hypoglycemic drugs
→ due to blocking of hepatic β_2 receptors glycogenolysis

4. α adrenergic blockers

1) Non selective

Phentolamine - Phenoxybenzamine

No longer used in the treatment of hypertension as they cause tachycardia, due to:
1. *Major mechanism* → blocking of presynaptic α_2 receptors so ⇑ NA release → tachycardia
2. *Minor mechanism* → Baroreceptor mediated reflex tachycardia to overcome hypotension

2) Selective α_1

Prazosin (Minipress®) - **Terazosin** (Itrin®) - **Doxazosin** (Cardura® - Dosin® - Doxacor®)

Pfizer
Minipress
2 mg
30 TABLETS

20 TABLETS
DOSIN®
Doxazosin
2 mg
EIPICO

Doxacor
2 mg
20 tablets

Pfizer
CARDURA
1 mg
21 Tablets

Mechanism of action

Selective competitive antagonists at α_1 receptors *(in smooth muscles of blood vessels)* causing vasodilatation → ⇓ blood pressure *(specially diastolic BP)*

α_1 blockers have beneficial effects on lipid profile
1. ⇑ **HDL** *(the good lipoprotein)*
2. ⇓ **LDL** *(the bad lipoprotein)*
3. ⇓ **Triglycerides**

Side effects

1. First dose phenomenon:
Hypotension - Fainting - Drowsiness - Loss of conciousness
2. Orthostatic hypotension
3. Failure of ejaculation
4. Diarrhea and abdominal cramps

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2) Vasodilators

1. Arterial vasodilators

- Hydralazine
- Minoxidil
- Diazoxide
- **Calcium channel blockers ex.** Verapamil - Nifedipine - Nicardipine - Amlodipine - Felodipine - Diltiazem

Mechanism of action

Relaxation of smooth muscles of arteries → vasodilatation → ⇓ peripheral resistance → ⇓ blood pressure

Hydralazine	**Release NO** leading to smooth muscle relaxation → vasodilatation
Minoxidil & Diazoxide	**Open K⁺ channels** leading to K⁺ outflux → hyperpolarization → smooth muscle relaxation → vasodilatation
Calcium channel blockers	**Block Ca^{+2} influx** so inhibit contraction → smooth muscle relaxation → vasodilatation

I) General side effects

1. Tachycardia and palpitations
Reflex tachycardia due to hypotension
Solution: co-administration of β blockers

2. Fluid retention
Due to increased renin activity *(due to hypotension)* → ⇑ angiotensin II → ⇑ aldosterone → ⇓ diuresis
Solution: co-administration of diuretics

3. Orthostatic hypotension - Headache - Dizziness

II) Specific side effects

Hydralazine

Lupus syndrome → Autoimmune disorder characterized by arthritis, myalgia, fever, skin rash, hepatospleenomegaly
it disappears after discontinuation of the drug

Minoxidil

It causes hypertrichosis (excessive hair growth) → on forehead, forearm.. etc so minoxidil is contraindicated with females
Can be used ***topically*** *to treat* ***alopecia***

PERFORMA
MINOXIDIL 5%
Hair Back

2. Mixed arterial and venous vasodilators

Sodium nitroprusside

Mechanism of action

Nitroprusside is metabolized to NO which activates guanyl cyclase → ⇑ **cGMP** → leading to *relaxation of smooth muscles in both arteries and veins:*
1. Vasodilatation of arteries → ⇓ afterload → ⇓ peripheral resistance → ⇓ diastolic blood pressure
2. Vasodilatation of veins → ⇓ preload → ⇓ venous return → ⇓ cardiac output → ⇓ systolic blood pressure

Side effects

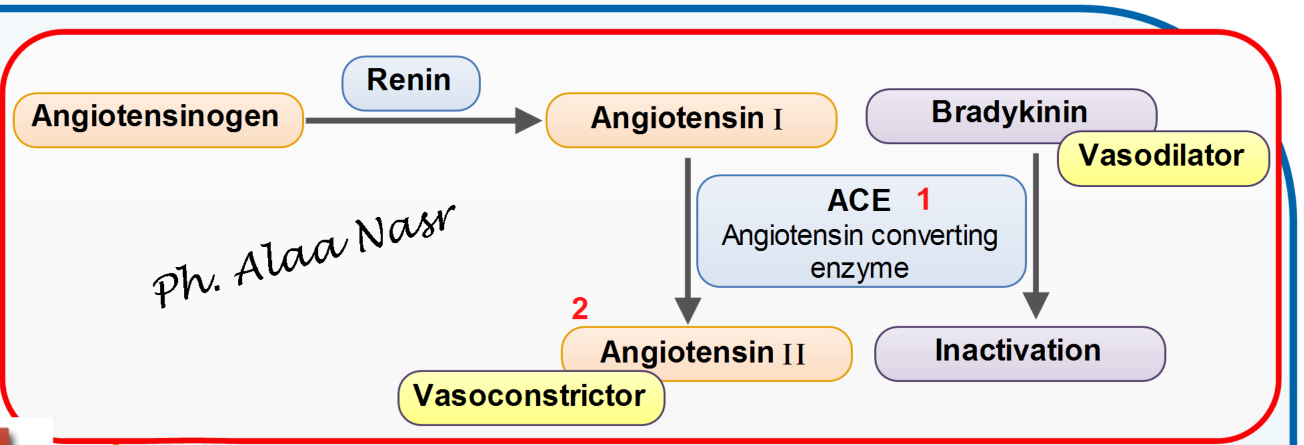
1. Nausea, vomiting, sweating, headache, tachycardia → due to severe hypotension
2. Prolonged administration leads to accumulation of **thiocyanate** *(the metabolic product of nitroprusside)* ***that may lead to***
a) *Mental disturbance*
b) *Thyroid abnormalities*

Uses

Hypertensive emergencies
a) Resistant / Refractory hypertension
b) Rebound hypertension

Nitroprusside is given by IV infusion (slow IV injecion) with close monitoring of blood pressure and thiocyanate level in the blood
its onset of action is 1 - 2 minutes

3) Drugs acting on renin angiotensin system (RAS)



Renin
Angiotensinogen → Angiotensin I
Bradykinin
Vasodilator
ACE 1
Angiotensin converting enzyme
2
Angiotensin II
Vasoconstrictor
Inactivation

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1. Angiotensin converting enzyme inhibitors (ACE inhibitors)

Captopril - Enalapril - Lisinopril

CAPOTEN
CAPOTRIL
CAPOZIDE
EZAPRIL
EZAPRIL-Co

Mechanism of action

Dual mechanism

Decrease formation of angiotensin II
⇓ vasoconstriction → ⇓ blood pressure
⇓ aldosterone → diuresis → ⇓ blood volume → ⇓ blood pressure

inhibit degradation of **bradykinin**
Vasodilatation

Side effects

1. Dry (non-productive) cough
- due to accumulation of bradykinins and may cause bronchospasm (contraction of bronchi)
- may require discontinuation of the drug
- Cough is more common in females

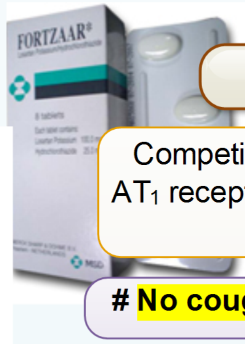
2 . Renal impairment
3. Skin rash and leucopenia

2. AT_1 receptor antagonists

Losartan - Valsartan - Candesartan

لوسارتان
Losartan
KANZAR 100
COZAAR
هيسارتان
Hysartan
HYZAAR

Tareg 160
NOVARTIS
Atacand 8 mg
CANDESAR



Mechanism of action

Competitive antagonists of Angiotensin II on AT_1 receptors in blood vessels → vasodilatation → ⇓ blood pressure

**No cough** as there is no effect on bradykynin

Renal physiology

The kidneys play an important role in maintaining the volume and composition of extracellular fluids by selective regulation of solute and fluid reabsorption

Each kidney is composed of 2 parts: **cortex and medulla**

Renal blood flow

Volume of the blood delivered to kidney per minute = 1200 ml/min

Glomerular filtration rate

- Volume of fluid filtered by renal glomerulus per minute = 90-120 ml/min = 170 liters/day
- About 99% of the filtrate is reabsorbed by renal tubules into the blood → so only 1.5 liters/day (from the filtered 170 liters/day) is excreted as urine

Nephron

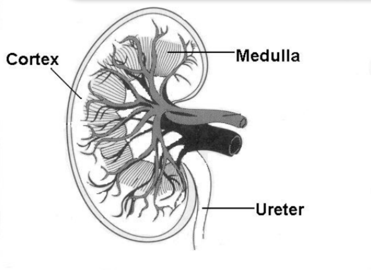
- The functional unit of excretion in kidneys is **nephron**
- Each kidney contains about 1 million nephrons

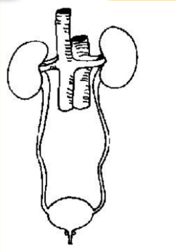
It consists of

1. Glomerulus
2. Proximal convoluted tubule
3. Loop of Henle
4. Distal convoluted tubule
5. Collecting tubule

4) Diuretics

Drugs that ⇑ urine output by ⇓ renal Na^+ reabsorption → loss of Na^+ and water in urine





Steps of excretion

1. Glomerular filtration

- Blood goes to the glomerulus through the afferent arteriole to be filtered *(by diffusion)* under high pressure in Bowman's capsule then blood is discharged to the efferent arteriole
- Small molecules and ions can easily pass to the filtrate
- Big molecules such as RBCs and plasma proteins (with any drugs bound to them) can not pass (not filtered)

2. Tubular reabsorption

The body discovers that it needs most of the materials that present now in the filtrate ! so reabsorption of Na^+, water and any needed material **from the tubule lumen to the blood** occurs

- It is done in nephron parts other than glomerulus

- **Each part of them has certain capacity of reabsorption process:**

1) **Proximal convoluted tubule** → reabsorption of **65%** of Na^+ ions
2) **Loop of Henle** → reabsorption of **25%** of Na^+ ions
3) **Distal convoluted tubule** → reabsorption of **6%** of Na^+ ions
4) **Collecting tubule** → reabsorption of **4%** of Na^+ ions

- As Na^+ reabsorption increase water reabsorption increase *(diuretics oppose this action partially)* → so Na^+ reabsorption is important to maintain blood volume

3. Tubular secretion

The body chooses to discharge some materials (as waste material) actively using carriers and energy **from the blood directly into the tubular lumen (filtrate)**

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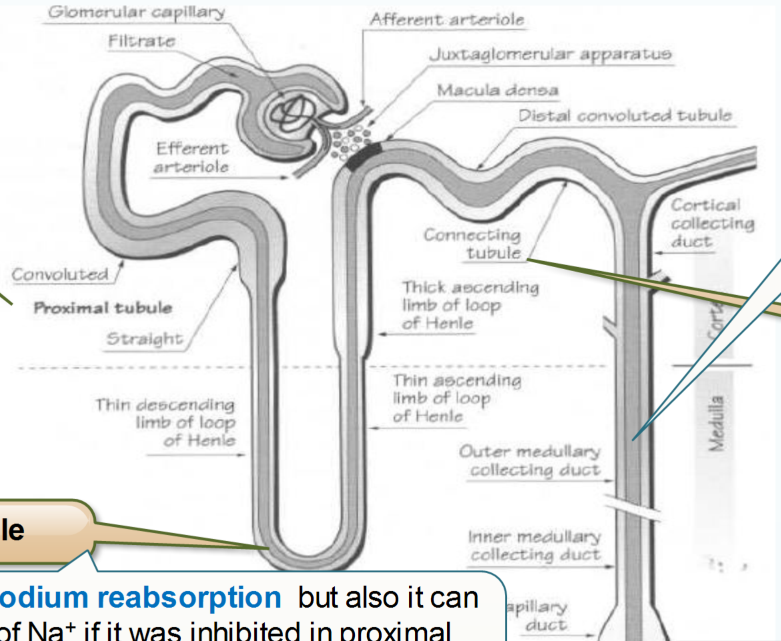
Each part process Na^+ reabsorption by certain mechanism as the following



1. Proximal convoluted tubule (PCT)

- Resposible for **reabsorption of 70-75% of filtrate** from urine to blood by high osmotic pressure of peritubular capillaries
- **65% of sodium is reabsorbed** as the concentration gradient between filtrate and blood is very high (high concentration of Na^+ in filtrate) so Na^+ moves from filtrate to blood by ***passive diffusion*** **by two transport systems:**

1) Symporter or co-transport

it is a carrier for reabsorption of two or more molecules in the same direction

→ *reabsorption of sodium with glucose or amino acid*

2) Antiporter

it is a carrier for exchange of two molecules in opposite directions

→ *reabsorption of sodium and excretion of H^+*

- Firstly Na^+ enters the cell of the lumen through an **antiport mechanism in exchange with H^+,** then it is discharged into the blood through **Na^+/K^+ ATPase pump**
- Then **H^+** (present in urine) will + bind to **HCO_3^-** (bicarbonate ion) to form → **Carbonic acid** → which dissociate to **CO_2 + water** (released in urine)
- **CO_2** diffuses to the blood and react with + **water** again to enter another cycle ... etc
- The binding an dissociation of CO_2 and water into Carbonic acid is mediated by **carbonic anhydrase enzyme** *(this enzyme is responsible for production of H^+ that helps Na^+ to enter the cell → if inhibited Na^+ will not be reabsorbed from this part of nephron)*

2. Loop of Henle

- It is normally causes **25% of sodium reabsorption** but also it can compensate the reabsorption of Na^+ if it was inhibited in proximal convoluted tubule
- **It consists of** descending limb, base and ascending limb

In descending limb

- Water can pass from the lumen to the blood till reaching the base
- Can not be targeted by diuretics

At the base

Water reabsorption stops due to → water reabsorption in the descending limb makes the filtrate too concentrated (high concentration of Na^+)

The ascending limb

- It contains a **Na^+ / K^+ / $2Cl^-$ carrier (symporter or co-transport)** which is responsible for **25% of sodium reabsorption**
- This process needs **energy** as it is *"active transport"*, this energy is obtained from **Na^+ / K^+ ATPase enzyme**

Here Ca^{+2} and Mg^{+2} pass freely to blood only when Na^+ ions are already in the blood (to create the potential difference needed for Ca^{+2} and Mg^{+2} to transfer)

3. Distal convoluted tubule (DCT)

Responsible for **reabsorption of 6% of sodium using Na^+ / Cl^- carrier (symporter or co-transport)**

It needs **energy** which is also obtained from **Na^+ / K^+ ATPase enzyme**

Here reabsorption of Na^+ is parallel with secretion of Ca^{+2} ions from the blood to urine

4. Collecting tubules (duct)

- Responsible for **reabsorption of 4% of sodium**
- **Collecting ducts are under hormonal control:**

1. Antidiuretic hormone (ADH) → responsible for **water** reabsorption

2. Aldosterone → **Na^+ reabsorption and K^+ secretion**

Classes of diuretics

1. Carbonic anhydrase inhibitors
2. Osmotic diuretics
3. Loop diuretics
4. Thiazide diuretics
5. Potassium sparing diuretics

1. Carbonic anhydrase inhibitors

Cidamex
250 mg tablets

Acetazolamide
Dichlorophenamide

Mechanism of action

Site of action: PCT

They inhibit **carbonic anhydrase enzyme** in PCT cells

Remember

$$CO_2 + H_2O \overset{CA}{\longleftrightarrow} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

Carbonic anhydrase enzyme is responsible for **reabsorption of Na^+ and HCO_3^-**

So inhibition of CA → increase excretion of Na^+ and HCO_3^- and water in urine **causing**

- **Alkaline urine**
- **Metabolic acidosis**

Carbonic anhydrase inhibitors have mild diuretic effect .. Why ?

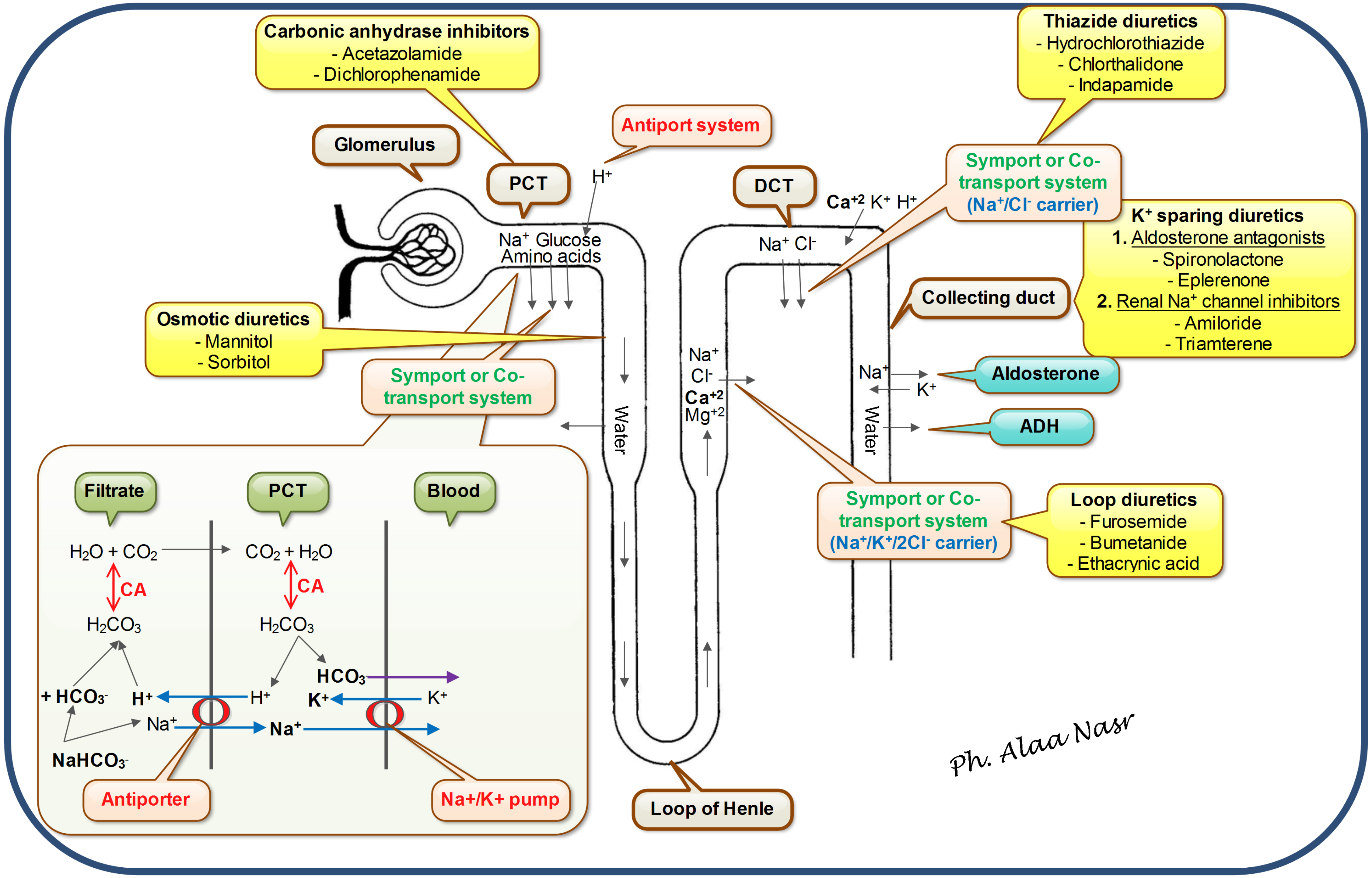
1. Na^+ that is not reabsorbed from PCT **can be reabsorbed** from both loop of Henle and DCT

2. Their effect is **self limiting within 2-4 days !** as increased loss of HCO_3^- in urine stimulates compensatory mechanisms for NaCl reabsorption

# Carbonic anhydrase is found inside cells of PCT and in the luminal membrane

We can improve carbonic anhydrase inhibitors diuretic effect .. How ?

1. By using it on alternative days
2. Given with supplementation of HCO_3^-



Carbonic anhydrase inhibitors
- Acetazolamide
- Dichlorophenamide

Thiazide diuretics
- Hydrochlorothiazide
- Chlorthalidone
- Indapamide

Antiport system

Symport or Co-transport system (Na⁺/Cl⁻ carrier)

K⁺ sparing diuretics
1. Aldosterone antagonists
   - Spironolactone
   - Eplerenone
2. Renal Na⁺ channel inhibitors
   - Amiloride
   - Triamterene

Osmotic diuretics
- Mannitol
- Sorbitol

Symport or Co-transport system

Symport or Co-transport system (Na⁺/K⁺/2Cl⁻ carrier)

Loop diuretics
- Furosemide
- Bumetanide
- Ethacrynic acid

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Therapeutic uses

1. Glaucoma ! inhibition of CA enzyme in ciliary body → decrease the formation of aqueous humor
(Topical CA inhibitor ex. dorzolamide (Xola®)

2. Urine alkalinization → increase elimination of weak acidic substances as in case of overdose or poisoning by Aspirin

3. Metabolic alkalosis *(as they cause acidosis) (specially when caused by other diuretics)*

4. Prophylaxis of mountain sickness used for 5 days to prevent pulmonary edema and cerebral edema

mountain sickness → hypoxia → pulmonary or cerebral edema → → using CA inhibitors → acidosis → increase respiration → preventing edema

Acetazolamide pharmacokinetics

1. Orally absorbed
2. Highly bound to plasma proteins 95%
3. Cross BBB and placenta
4. Secreted in breast milk
5. Excreted by organic acid secretory carriers (renal tubular secretion)

Adverse effects

1. **Metabolic acidosis**
2. **Hypokalemia**
3. **Hypersensitivity** reactions due to sulpha group causing fever, rash and bone marrow suppression
4. **Renal stones** as they increase excretion of Ca^{+2} and PO_4^{-3} in urine (calcium is insoluble in alkaline urine leading to stone formation)
5. **Teratogenic** (in animal studies) so **contraindicated during pregnancy**

Carbonic anhydrase inhibitors should be **avoided in patients with hepatic cirrhosis** as these drugs **decrease the excretion of NH^{+4}** so ammonia may reach the brain causing **encephalopathy**

2. Osmotic diuretics

Mannitol (IV)
Sorbitol (IV)

Mechanism of action

- **Site of action:** PCT and descending limb of loop of Henle
- They are freely filtered in Bowman's capsule then goes to proximal convoluted tublues → **increase osmolarity of urine** so attract water preventing its reabsorption → increase water loss in urine
- They have **no effect on Na^+** transport in nephron

# Presence of osmotic diuretics in blood → increases osmolarity of blood → so attracts water from tissues → leading to temporarily increase in blood volume

Therapeutic uses

1. Cerebral edema
2. Glaucoma → in acute attack or before surgery
3. Washing of kidney *(rapid removal of renal toxins)*

Adverse effects

1. Hypotension
2. Reflex tachycardia
3. Extracellular volume expansion (temporarily) **that can worsen heart failure**

3. Loop diuretics High ceiling diuretics

Furosemide
Bumetanide
Ethacrynic acid

Lasix
40mg
Furosemide
Saluretic
24 Tablets
Aven
Burinex
1mg
Bumetanide
Lafurex
Furosemide
20 mg.

They are the most powerful diuretics → as Na^+ **(25%)** loss can not be compensated by the following parts of nephron → leading to very high loss of Na^+ and water in urine → that is way they are called "high ceiling diuretics"

Mechanism of action

- **Site of action:** ascending limb of loop of Henle where **25%** of Na^+ is reabsorbed

1. They inhibit $Na^+/K^+/2Cl^-$ co-transporter → decrease reabsorption of Na^+
2. Increase expression of **COX 2** *(cyclo-oxygenase enzyme 2)* → **increase synthesis of PGs** *(prostaglandines)*

- causes vasodilatation of renal blood vessels → increase renal blood flow → increase glomerular filtration and urine flow
- decrease water reabsorption *(this effect appers in patients with nephrotic syndrome and hepatic cirrhosis)*

***# Remember:* NSAIDs inhibit sythesis of PGs**

- Here as we said before, due to normal reabsorption there will be a certain normal voltage that causes Ca^{+2} and Mg^{+2} ions to move from the tubular lumen to the blood through interstitial spaces
- so, by using **loop diuretics** → Na^+ and K^+ reabsorption are inhibited leading to → **inhibition of Ca^{+2} and Mg^{+2} reabsorption** *(loss of them in urine !)*

Therapeutic uses

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1. Edema associated with
- heart failure or
- liver cirrhosis

2. Emergencies *(due to rapid action)* → in acute pulmonary edema
3. Hypercalcemia *(accelerate calcium excretion)*

• Furosemide pharmacokinetics

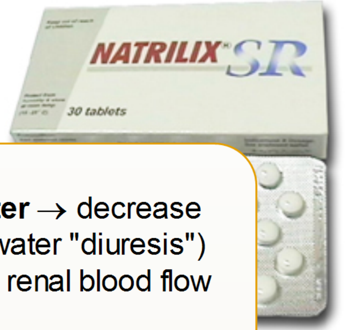
1. Orally absorbed
2. Excreted by tubular secretion using carrier for excretion of organic acids *(can be inhibited by NSAIDs and probenicid leading to decrease excretion of furosemide)*

Adverse effects

1. Overdose causes hypovolemia (⇓ blood volume) **leading to orthostatic hypotension**
2. Hypokalemia, hypocalcemia and hypomagnesemia
3. Metabolic alkalosis
4. Hyperuricemia *(due to competetion for carrier of tubular excretion of uric acid)*
5. Allergic reaction
6. Ototoxicity usually reversible deafness the risk increases with co-administration of aminoglycosides *(Ethacrynic acid causes irreversible deafness)*

4. Thiazide diuretics

Hydrochlorothiazide
Chlorthalidone
Indapamide

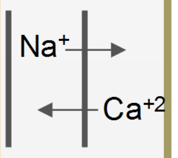


Mechanism of action

- **Site of action:** DCT

1. They inhibit Na^+/Cl^- co-transporter → decrease reabsorption of Na^+ (loss of Na^+ and water "diuresis")
2. Direct vasodilatation → increase renal blood flow so increase urine flow
so as we see, thiazides are very effective in hypertension

- Normally as we said before → in DCT Na^+ reabsorption is accompanied by Ca^{+2} excretion in urine by antiport system
- so, when thiazides inhibit Na^+ reabsorption they **decrease Ca^{+2} excretion in urine** (hypercalcemia)



Therapeutic uses

1. Hypertension *(notice that.. lowdose of indapamide decreases blood pressure with minimal diuretic effect)*
2.Edema associated with
- heart failure or
- liver cirrhosis
- Premenstrual tension

# Used with patients susceptible to kidney stones *(as they do not cause Ca^{+2} excretion in urine)*

• Chlorothazide pharmacokinetics

1. Slowly absorbed orally
2. Only thiazide available for parenteral administration
3. Excreted by tubular secretion using carrier for excretion of organic acids

Adverse effects

1. Hypokalemia
2. Metabolic alkalosis
3. Hyperglycemia (decrease insulin secretion)
4. Hypersensitivity (due to sulpha group)
5. Hyperuricemia
6. Hyperlipidemia
7. impotence

Hypokalemia

Etiology

- Serum K+ level falls below 2.5 mEq / L *(normal value 5 mEq / L)*
- **Hypokalemia occurs with loop and thiazide diuretics.. How?**
- They prevent Na^+ reabsorption so increase Na^+ delivered to collecting duct where K^+ is excreted in exchange with Na^+ → leading to increase K^+ loss in urine (hypokalemia)

Symptoms

1. Muscle weakness
2.Neurological symptoms (drowsiness, irritability, confusion, loss of sensation, coma)
3. Arrhythmia
4. Tetany (muscle contractions)
5. Respiratory arrest

Treatment

1. Oral supplementation of KCl with monitoring of serum K^+ concentration

2. Consumption of K^+ reach food such as banana - dates - orange - grapefruit

3. Combination with K^+ sparing diuretics

5. Potassium sparing diuretics

1) Aldosterone antagonists

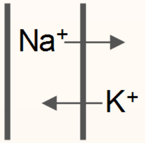
Spironolactone
Eplerenone

Mechanism of action

- **Site of action:** late DCT and collecting tubules
- **They are competitive antagonists of aldosterone receptors** causes inhibition of Na^+ reabsorption *(lost in urine - diuresis)*

What does aldosterone hormone normally do ?

1. Activation of Na^+ channels → leading to Na^+ reabsorption
2. Increase synthesis of Na^+/K^+ ATPase → leading to **activation of Na^+ pump** → Na^+ reabsorption



Therapeutic uses

1. Moderate diuretic effect → so combined with thiazides or loop diuretics
2. Used in cases of excess aldosterone secretion
a) 1^{ry} cause → ***Cronn's disease***
b) 2^{ry} causes→ heart failure - nephrotic syndrome - cirrhosis

So we need to know that these drugs are **not effective** in patients with decreased secretion of aldosterone from adrenal cortex → ***Addison's disease***

Adverse effects

1. Hyperkalemia
2. Metabolic acidosis
3. Peptic ulcer
4. Antiandrogen (gynecomastia and impotence in males)
5. Antiprogesterone (menstrual irregularities in females)

Notice that Eplerenone has less blocking effect than Spironolactone to androgen and progesterone receptors

2) Renal Na^+ channel blockers

Amiloride
Triamtrene

Mechanism of action

- **Site of action:** late DCT and collecting tubules
- **They block Na^+ channels** decreasing Na^+ reabsorption *(lost in urine - diuresis)*
- **They are not dependent on aldosterone** → so *can be used for patients with* ***addison's disease***

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Adverse effects

1. Hyperkalemia
2. Metabolic acidosis
3. Kidney stones as triamtrene is slightly soluble
4. Acute renal failure could be resulted from combination of **triamterene and indomethacin**

Combinations of K^+ sparing diuretics and K^+ wasting diuretics

1. Amiloride + Hydrochlorothiazide → Moduretic®, Yostiretic®
2. Spironolactone + Hydrochlorothiazide → Aldactazide®
3. Spironolactone + Furosemide → Lasilactone®

It is better to give each drug alone

Lasilactone
50 mg
Aventis

Aldactazide

Yostiretic

MODURETIC
MSD